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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,532	12/11/2003	Julian Edward Sale	18396/2002B	9057
29933	7590	10/18/2006	EXAMINER	
PALMER & DODGE, LLP KATHLEEN M. WILLIAMS 111 HUNTINGTON AVENUE BOSTON, MA 02199			SULLIVAN, DANIEL M	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/733,532

Applicant(s)

SALE ET AL.

Examiner

Daniel M. Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006 and 11 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-12 and 14-31 is/are pending in the application.
- 4a) Of the above claim(s) 17-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 14-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This Office Action is a reply to the Papers filed 15 May 2006 and 11 August 2006 in response to the Non-Final Office Action mailed 14 November 2005. Claims 17-31 were withdrawn from consideration and claims 1-16 were considered in the 14 November Office Action. Claim 13 was cancelled and claims 1, 3, 5, 6, 10-12 and 14 were amended in the 11 August Paper. Claims 1-12 and 14-31 are pending and claims 1-12 and 14-16 are under consideration.

#### ***Response to Amendment and Arguments***

##### **Sequence Compliance**

Applicant's statement directing entry of the sequence listing filed 13 September 2004 in the remarks filed 15 May 2006 (at p. 4) is acknowledged.

##### **Claim Rejections - 35 USC § 112**

Rejection of claims 1-6 and 8-16 under 35 U.S.C. 112, first paragraph, as lacking enablement for a method for preparing a cell line capable of constitutive hypermutation of a target nucleic acid region wherein said cell line is prepared from a cell line other than an B cell line is **withdrawn**. Applicant argues persuasively that any cell could be screened for ongoing target sequence diversification according to the method.

Claims 1-12 and 14-16 **stand rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preparing an immunoglobulin expressing cell line capable of directed constitutive hypermutation of target sequence wherein the rate of mutation in the cell is modulated by administering a mutagen or homozygous deletion of XRCC2 or XRCC3, does not reasonably provide enablement for the method wherein the rate of mutation is modulated by expression of any sequence modifying gene product or any gene deletion, conversion or insertion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This rejection was previously applied to claims 14-17 and is newly applied to claims 1-12 in view of the amendment of claim 1 such that the genetic manipulation is now limited to gene deletion, conversion and insertion. As discussed in the previous Office Action, although the relative level of skill in the art is high, the skilled artisan would not be able to practice the full scope of the claimed invention without having to engage in undue experimentation. The specification and art provide ablation of XRCC2 and XRCC3, two closely related genes, as the only established gene deletion, conversion or insertion useful in the claimed method of preparing a cell line capable of directed constitutive hypermutation. In the paragraph bridging pp. 7-8, the previous Office Action cites Sale et al. as teaching that ablation of Rad51 paralogs increased somatic hypermutation while ablation of the closely related genes Rad54 and Rad52 had no effect. Thus, Sale et al. demonstrates the general unpredictability of modulating the rate of mutation in a cell by deletion, conversion or insertion of specific genes. In view of this, one of ordinary skill would have no basis to distinguish those manipulations likely to be useful in the

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claimed method from those that would not be useful. Therefore, the skilled artisan would have to resort to empirical experimentation to identify manipulations that could be used in the method.

Given the tremendous scope of the claims, which embrace modulation of the rate of mutation by deletion, conversion or insertion of any gene, this would clearly require that the skilled artisan engage in undue experimentation to identify the operative embodiments of the claimed invention.

#### *Response to Arguments*

In response to the *prima facie* rejection of record, Applicant contends that the claims are not overly broad because they are now limited to methods of genetic manipulation that were well within the grasp of one of ordinary skill in the art at the time the application was filed.

This argument has been fully considered but is not deemed persuasive. Although processes of gene deletion, conversion and insertion were known in the art at the time the application was filed, to the extent that the claims embrace targeted deletion, conversion and insertion, the skilled artisan would not know which genes to manipulate. In view of the state of the art, which demonstrates that the effect of manipulating even closely related genes on mutation rate is unpredictable, the skilled artisan would not be able to practice the full scope of a method that broadly encompasses deletion, conversion or insertion of any gene without engaging in undue experimentation to identify which genes to manipulate and how (i.e., deletion, conversion or insertion) to manipulate them.

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Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph.

Rejection of claims 1-12 and 14-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the claim amendments.

#### Double Patenting

Claims 1-12 **stand rejected** under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 36, 37, 39 and 40 of copending Application No. 10/146,505 (now U.S Patent No. 7,122,339) in view of Monteiro *et al.* (2000) *Teratogen. Carcinogen. Mutagen.* 20:357-386 for the reasons set forth in the previous Office Action (pp. 12-13). In the 15 May remarks, Applicant states that a terminal disclaimer effective to obviate the double patenting rejection will be filed upon notification of allowable subject matter, which is acknowledged. However, until such time as a terminal disclaimer is filed, the claims stand rejected. Note that, in view of the fact that the Application has now issued as a patent, this rejection is no longer provisional.

#### Claim Rejections - 35 USC § 102

Claims 1-12 stand rejected under 35 U.S.C. 102(b) as being anticipated by Sale *et al.* (April 2000) WO 00/22111 (made of record in the IDS filed 11 December 2003) for the reasons

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set forth in the 14 November Office Action (pp. 14-15) and herein below in the response to Applicant arguments.

*Response to Arguments*

In response to the *prima facie* rejection of record, Applicant contends that Sale et al. does not teach genetic manipulation by gene deletion, conversion or insertion. (Remarks filed 15 May, p. 7.)

This argument has been fully considered but is not deemed persuasive. As stated in the previous Office Action, “claim 10 of Sale et al., which depends from each of the preceding claims recites that the rate of mutation in the cell is modulated by the administration of a mutagen”. The specification provides no limiting definition of what constitutes a gene “conversion” and, absent evidence to the contrary, any modification of the rate of mutation in a cell by the administration of a mutagen would result from conversion of a gene in some fashion. Likewise, gene deletion can be broadly construed as encompassing functional, as well as physical, deletion of the gene, which could result from the administration of a mutagen. Therefore, at least insofar as the claims encompass gene conversion and deletion by any means, the claims remain anticipated by the teachings of Sale et al.

Applicant’s arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §102(b) as anticipated by the art.

***Conclusion***

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

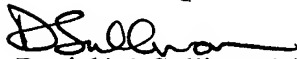
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Daniel M. Sullivan, Ph.D.

Primary Examiner

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